UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY

AND POLLUTION PREVENTION

MEMORANDUM

DATE: October 17, 2017

SUBJECT: **Noviflumuron**: Report of the Cancer Assessment Review Committee

PC Code: 118204
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
TXR No.: 0057626
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A

CAS No.: N/A
40 CFR: N/A

FROM: Sarah Dobreniecki, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Gregory Akerman, Co-Chair
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Cancer Assessment Review Committee
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TO: Whang Phang, Toxicologist
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The Cancer Assessment Review Committee met on August 2, 2017 to re-evaluate the cancer classification of noviflumuron in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached is the final Cancer Assessment Document.

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

Noviflumuron (XDE-007)

October 12, 2017

CANCER ASSESSMENT REVIEW COMMITTEE

HEALTH EFFECTS DIVISION

Office of Pesticide Programs

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Cancer Assessment Review Committee (CARC) met on August 2, 2017, to evaluate the cancer classification of noviflumuron (XDE-007) in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). The results from the chronic toxicity/carcinogenicity study in rats, the carcinogenicity study in mice, metabolism and mutagenicity studies, as well as structure activity relationships were presented to the committee.

In a mouse carcinogenicity study (MRID 46539601), XDE-007 (Noviflumuron; 97.9% a.i.; Lot No. F0031-161) was administered in the diet to CD-1 mice (50/sex/dose) for up to 18 months. The doses were 0, 0.5, 3.0, and 30.0 mg/kg/day in males and 0, 0.5, 30.0, and 100 mg/kg/day in females. The results demonstrated the following tumor incidences:

In male mice, there was an increased incidence of liver tumors at the high dose (30 mg/kg/day). This increase showed statistically significant trends for hepatocellular adenomas and hepatocellular adenomas and/or carcinomas combined, both at $p < 0.05$. There were no significant pairwise differences between any of the dosed groups and the controls. The liver tumors in male mice were not considered treatment-related since there was a lack of significant pairwise comparisons for adenomas or carcinomas; this is a common tumor in aged mice; and the lack of pre-neoplastic lesions in the liver. It is also unclear whether the incidence values at the high dose are outside the historical control range.

In female mice, there was an increased incidence of liver and lung tumors at the high dose (100 mg/kg/day). The liver tumors showed statistically significant trends for hepatocellular adenomas and hepatocellular adenomas and/or carcinomas ($p<0.05$); there was also a significant pairwise difference between the high dose group and the controls for hepatocellular adenomas ($p<0.05$) and for hepatocellular adenomas and/or carcinomas combined ($p<0.01$). There was an increase in lung tumors in high dose females also, but the increase was not considered treatment-related due to lack of statistical trend or pairwise comparison. Furthermore, there were no relevant non-neoplastic treatment-related effects in the lung, no clear data to indicate that increased lung tumor incidence was outside of the historical control range for this tumor type, and no significant increase in the incidence of lung tumors was seen in male mice.

In a combined chronic toxicity/carcinogenicity study (MRID 46542901), XDE-007 (Noviflumuron; 97.9% a.i.; Lot Nos. F0031-161 and F0031-148) was administered in the diet to Fischer 344 rats (65/sex/dose) at nominal dosages of 0, 0.1, 1.0, 75, or 300 mg/kg/day for up to 2 years. After one year, an interim sacrifice was performed on 10 rats/sex/dose. Increases in the following tumors were found.

In male rats, a treatment-related increase in hepatocellular adenomas and combined hepatocellular adenomas and carcinomas were found in high dose males (300 mg/kg/day); the tumor incidence demonstrated statistical significance in both pairwise comparison (high dose) and trend test ($p<0.01$). Three cases of mesotheliomas were noted in high dose males, but were not considered treatment-related due to lack of significant pairwise difference in incidence between any of the treatment groups and the controls, they were within the historical control range, they

are a common tumor type in male rats, and there were no relevant non-neoplastic lesions to support a treatment effect.

In female rats, there was an increase in the incidence of endometrial stromal polyps in 75 and 300 mg/kg/day based on statistical significance in both pair-wise comparison and trend test ($p<0.01$), and the incidence was greater than the historical and concurrent controls. Increased incidence of uterine mass/nodules were also apparent.

The CARC concluded the following in its weight of evidence evaluation of the available data:

- Noviflumuron produced treatment-related hepatocellular adenomas and hepatocellular adenomas and/or carcinomas combined in CD-1 female mice.
- In male Fischer 344 rats, noviflumuron induced a treatment-related increase in hepatocellular adenomas and combined hepatocellular adenomas and carcinomas.
- Noviflumuron induced treatment-related uterine tumors (endometrial stromal polyps) in female Fischer 344 rats.
- There is no concern for mutagenicity. The available mutagenicity studies for noviflumuron were negative.
- The closest analogs to noviflumuron are novaluron, lufenuron, and hexaflumuron. These three analogs have been shown previously to be non-carcinogenic.
- No mode of action (MOA) data are available for any of the treatment-related tumors.

In accordance with EPA's Final Guidelines for Carcinogenic Risk Assessment (2005), CARC classified noviflumuron as "Likely to be Carcinogenic to Humans" based on the occurrence of treatment-related liver tumors in female mice and male rats, and the occurrence of uterine tumors (endometrial stromal polyps) in rats.

The CARC recommended a linear low-dose extrapolation model (Q1*) for the human cancer risk assessment.

I. BACKGROUND

Noviflumuron is a benzoylphenylurea insect growth regulator that acts through disruption of chitin synthesis in developing termites. It is used as bait around ornamental trees, buildings, wood decks, wood fences, and wood utility poles to control subterranean termites and as an indoor crack and crevice treatment to control cockroaches. Noviflumuron products are only formulated as ready-to-use gel baits in syringe applicators, and as an impregnated bait station. The labels specify that only pest management professionals licensed by the state to apply termite control products may use noviflumuron. It is considered a non-food use pesticide. Hence, handler and post-application exposures are expected to be negligible.

II. EVALUATION OF CARCINOGENICITY STUDIES

1. Carcinogenicity Study in Mice

Citation: Johnson, K.A. (2005) XDE-007: 18-month oncogenicity study in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 021038, April 25, 2005. MRID 46539601. Unpublished.

A. Experimental Design

In a mouse carcinogenicity study (MRID 46539601), XDE-007 (Noviflumuron; 97.9% a.i.; Lot No. F0031-161) was administered in the diet to CD-1 mice (50/sex/dose) for up to 18 months. The doses were 0, 0.5, 3.0, and 30.0 mg/kg/day in males and 0, 0.5, 30.0, and 100 mg/kg/day in females. Following 78 weeks of exposure, all surviving animals were euthanized and subjected to necropsy.

B. Survival

In male mice, there were no statistically significant survival disparities among the dose groups (Table 1), while there was a statistically significant increasing trend and pairwise comparison for mortality in female mice (Table 2).

Table 1. Noviflumuron – CD-1 Mouse Study (MRID No. 46539601)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks			Total
	1-26	27-52	53-79[f]	
0	0/50	1/50	10/49	11/50 (22)
0.5	0/50	1/50	9/49	10/50 (20)
3.0	0/50	2/50	8/48	10/50 (20)
30.0	0/50	0/50	11/50	11/50 (22)

+Number of animals that died during the interval/Number of animals alive at the beginning of the interval.
[f] Final sacrifice at week 79.

( ) Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Noviflumuron – CD-1 Mouse Study (MRID No. 46539601)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks			Total
	1-26	27-52	53-80[f]	
0	0/50	2/49[a]	12/47	14/49 (29)**
0.5	0/49[b]	0/49	8/49	8/49 (16)
30.0	0/50	2/50	6/48	8/50 (16)
100.0	5/50	8/45	15/37	28/50 (56)**

+Number of animals that died during the interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at weeks 79-80.
[a]One accidental death at week 52 in the control group.
[b]One accidental death at week 4 in the 0.5 mg/kg/day dose group.
( ) Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Tumor Analysis

Males

In male mice, there was an increased incidence of liver tumors. This increase showed statistically significant trends for hepatocellular adenomas and hepatocellular adenomas and/or carcinomas combined, both at $p < 0.05$. There were no significant pairwise differences between any of the dosed groups and the controls. The statistical analyses of the tumors in male mice were based upon Fisher's Exact Test and the Exact Test for Trend (Table 3). The historical control data are limited, and provide little confidence for the purpose of comparison, particularly for combined adenomas and/or carcinomas for which the data are derived from only a single study.

The incidence of liver tumors in male mice was not considered treatment-related based on the following: there was a lack of significant pairwise comparisons for adenomas or carcinomas; this is a common tumor in aged mice; and there were no pre-neoplastic lesions. It is also unclear whether the incidence values at the high dose are outside the historical control range.

Table 3. Noviflumuron – CD-1 Mouse Study (MRID No. 46539601)

Male Liver Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	0.5	3.0	30.0	Historical Controls (n=50) [c]
Adenomas	5[a]/50	5/50	2/50	10/50	0-8
(%)	(10)	(10)	(4)	(20)	(0-16%)
P =	0.0208*	0.6297	0.9441	0.1312	
Carcinomas	0/50	2/50	2/50	2[b]/50	0-9
(%)	(0)	(4)	(4)	(4)	(0-18%)
P =	0.2213	0.2475	0.2475	0.2475	
Combined	5/50	7/50	4/50	12/50	9[d]
(%)	(10)	(14)	(8)	(24)	(18%)
P =	0.0165*	0.3798	0.7565	0.0542	

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 37.
[a]First adenoma observed at week 37 in the control group.
[b]First carcinoma observed at week 74 in the 30 mg/kg/day dose group.
[c] Range of 3 carcinogenicity studies conducted with CD-1 mice for the performing lab since 12/2001.
[d] The number of control mice with adenoma or carcinoma were not reported in 2 studies, and the number in the 3rd study was 9.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Females

In female mice, there was an increased incidence of liver and lung tumors at the high dose (100 mg/kg/day); the statistical analyses of these tumors in female mice were based upon Peto's Prevalence Test. The liver tumors showed statistically significant trends for hepatocellular adenomas and hepatocellular adenomas and/or carcinomas, both at $p < 0.01$ (Table 4). There was also a significant trend for hepatocellular carcinomas at $p < 0.05$. There were significant pairwise differences between the 100 mg/kg/day dose group and the controls for hepatocellular adenomas at $p < 0.05$ and for hepatocellular adenomas and/or carcinomas combined at $p < 0.01$.

For bronchiolar-alveolar carcinomas in high-dose females (100 mg/kg/day), a significant trend at $p < 0.01$ and a significant pairwise comparison of the high dose group at $p < 0.05$ were present (Table 5). The incidence of bronchiolar-alveolar adenomas and combined bronchiolar-alveolar adenomas and carcinomas at the high dose were comparable to the concurrent control group, and no dose-related response was found. Interpretation of these findings was based on the following considerations: (1) no relevant non-neoplastic treatment-related effects in the lung were observed; (2) the distinction between bronchiolo-alveolar adenomas and carcinomas is often unclear,

increasing the weight of the combined incidence here; (3) the pairwise p-value for the carcinomas in the high-dose group vs control group was influenced by the lower number of animals examined in the high-dose group (n=22). (If an n of 38 were used for carcinomas, as for lung adenomas, then the group difference is no longer statistically significant); and (4) it is unclear whether the incidence values at the high dose are outside the historical control range. A compound-related increase in lung tumor incidence was not seen in the males.

It should be noted that when considering the tumor incidence in male and female mice, there were disparities in both high doses tested and survival rates. In male the highest dose tested was 30 mg/kg/day, whereas in female it was 100 mg/kg/day. There was no difference in survival rate in males compared to the controls. In contrast, in the females, the highest dose group (100 mg/kg/day) showed a decrease in survival rate (56% vs 29% in the control group).

In summary, the increase in liver adenomas and combined adenomas and carcinomas in female mice was considered to be treatment-related at 100 mg/kg/day. The increased incidence of lung tumors was not considered to be treatment-related due to lack of statistical significant trend or pairwise comparison for the combined lung adenomas and carcinomas and other considerations noted above.

Table 4. Noviflumuron – CD-1 Mouse Study (MRID No. 46539601)

Female Liver Tumor Rates[+] and Peto's Prevalence Test Results

Dose (mg/kg/day)	0	0.5	30.0	100.0	Historical Controls (n=50) [c]
Adenomas	0/35	1[a]/41	0/42	3[a]/22	0-3
(%)	(0)	(2)	(0)	(14)	(0-6%)
P =	0.00183**	0.17776	-	0.01305*	
Carcinomas	0/35	0/41	0/42	1[b]/22	0
(%)	(0)	(0)	(0)	(5)	
P =	0.01585*	-	-	0.10360	
Combined	0/35	1/41	0/42	4/22	0-3
(%)	(0)	(2)	(0)	(18)	(0-6%)
P =	0.00017**	0.17776	-	0.00476**	

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a]First adenoma observed at the final sacrifice simultaneously in the 0.5 and 100 mg/kg/day dose groups.
[b]First carcinoma observed at the final sacrifice in the 100 mg/kg/day dose group.
[c] Range of 3 carcinogenicity studies conducted with CD-1 mice for the performing lab since 12/2001.

Note: Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 5. Noviflumuron – CD-1 Mouse Study (MRID No. 46539601)

Female Lung Tumor Rates+ and Peto's Prevalence Test Results

Dose (mg/kg/day)	0	0.5	30.0	100.0	Historical Controls (n=50) [c]
Adenomas	11/48	10/49	15/48	10[a]/38	0-7
(%)	(23)	(20)	(31)	(26)	(0-14%)
P =	0.20852	0.71200	0.26028	0.35581	
Carcinomas	0/35	0/41	1[b]/42	2[b]/22	0-4
(%)	(0)	(0)	(2)	(9)	(0-8%)
P =	0.00488**	-	0.18066	0.03594*	
Combined	11/48	10/49	16/48	12/38	
(%)	(23)	(20)	(33)	(32)	
P =	0.06780	0.71200	0.19913	0.16859	

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.
[a]First adenoma observed at week 51 in the 100 mg/kg/day dose group.
[b]First carcinoma observed at the final sacrifice simultaneously in the 30 and 100 mg/kg/day dose groups.
[c] Range of 3 carcinogenicity studies conducted with CD-1 mice for the performing lab since 12/2001.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

D. Non-Neoplastic Findings

An increased incidence of persistent tonoclonic convulsions was seen in 100 mg/kg/day females; a slight increase in tonoclonic convulsion was also observed in 30 mg/kg/day males (Table 6). In females, convulsions were first observed on day 43 and last seen on day 533. The 100-mg/kg/day females had a much higher incidence than all other groups for most of the clinical examination times, with the peak response occurring in 18 mice with tonoclonic convulsions on day 323. The convulsions in high-dose females tended to last longer, were more severe for the uncontrolled motions, and had a longer post-convulsion recovery period. Convulsion was also noted in 300- and 1000-mg/kg/day males and females in a 90-day oral toxicity study conducted in 2002 (Yano and Day, 2002). However, convulsion was determined not to be a cause of death in the 90-day study; it was also the case for the chronic/carcinogenicity study.

Table 6. Incidence (# affected/# examined [%]) of tonoclonic convulsion in mice treated with XDE-007 in the diet for up to 80 weeks.

Day	Dose (mg/kg/day in M/F)			
	0/0	**0.5/0.5**	**3/30**	**30/100**
Males				
113	0/50 (0)	0/50 (0)	1/50 (2)	3/50 (6)
337	2/49 (4)	1/50 (2)	0/48 (0)	7/50 (14)
505	2/45 (4)	1/45 (2)	2/45 (4)	1/44 (2)
Total Animal Days	15	18	4	24
Females				
43	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
323	1/49 (2)	1/49 (2)	1/50 (2)	18/38 (47)
533	1/38 (3)	4/44 (9)	0/43 (0)	3/24 (12)
Total Animal Days	32	36	27	156

In the liver, very slight to slight centrilobular/midzonal hepatocyte hypertrophy was observed in the ≥ 3-mg/kg/day males and the 100-mg/kg/day females (Table 7). Additionally, very slight diffuse panlobular hepatocyte hypertrophy was also observed in the 100-mg/kg/day females (3/50 treated vs 0/50 controls). Gross pathology data indicated an increase in the incidence of hepatic mass-nodules in high dose males.

In the lung, very slight to moderate subacute to chronic inflammation was increased in the ≥ 3-mg/kg/day males. In the ≥ 30-mg/kg/day females, the incidences of focal or multifocal aggregates of alveolar macrophages were increased and were significant ($p \leq 0.05$) at 100 mg/kg/day for multifocal aggregates. Additionally, an increased incidence of generalized congestion was noted in the 100 mg/kg/day females.

Table 7. Incidence of selected non-neoplastic microscopic findings in mice treated with XDE-007 in the diet for up to 80 weeks. [a]

Microscopic lesion		Dose (mg/kg/day in M/F)			
		0/0	0.5/0.5	3/30	30/100
Males (n=50)					
Liver	Hypertrophy, hepatocyte, centrilobular/midzonal (total)	14	16	21	30*
Lung	Inflammation, subacute to chronic, focal (total)	2	3	5	5
	Inflammation, subacute to chronic, multifocal (total)	0	3	1	6
Females (n=50)					
Liver	Hypertrophy, hepatocyte, centrilobular/midzonal (total)	4	0	4	11
	Hypertrophy, hepatocyte, panlobular, diffuse, very slight (total)	0	0	1	3
Lung	Aggregates of alveolar macrophages, focal (total)	0	0	4	4
	Aggregates of alveolar macrophages, multifocal (total)	0	1	4	6*
	Congestion: generalized (total)	0	0	0	4

* Significantly different from controls; $p \leq 0.05$

E. Adequacy of Dosing for Carcinogenicity Assessment

The CARC considered the doses in the mouse carcinogenicity study to be adequate and not excessive to assess carcinogenicity based on the following:

- In 2002, DOW AgroSciences met with HED to discuss proposed dose selections for a chronic/carcinogenicity study in Fischer 344 rats, a neurotoxicity study in the rat, and a carcinogenicity study in CD-1 mice (TXR 0050628, D281517; April 4, 2002). HED concluded that the dose levels selected for this study were reasonable and supported by the data presented by DOW AgroSciences at the meeting.

- An increase in both absolute and relative liver weights and associated finding of hepatocyte hypertrophy were seen in high dose males (30 mg/kg/day) and females (100 mg/kg/day) in the carcinogenicity study. The increases in liver weight and liver hypertrophy in association with liver tumors were considered by CARC to support the adequacy of the dosing for this study.

- In females treated at 100 mg/kg/day, an increased incidence of tonoclonic convulsions was observed for an extended period throughout the study (day 43 to day 533). A slight increase in tonoclonic convulsion was also seen in high dose males (30 mg/kg/day). The 100 mg/kg/day dose that induced tonoclonic convulsions was not considered excessive because animals recovered and survived to the end of the study.

Furthermore, the tonoclonic convulsions did not affect body weights or food consumption.

- In the lungs, focal and multifocal inflammation were seen in high-dose males and aggregated alveolar macrophages focal and multifocal in high-dose females.

2. Combined chronic toxicity/carcinogenicity study in rats

Citation: Yano, B.L., M.D. Dryzga, J. Thomas (2005) XDE-007: Two-year dietary chronic toxicity/oncogenicity and chronic neurotoxicity study in Fischer 344 rats. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 011168, April 22, 2005. MRID 46542901. Unpublished.

A. Experimental Design

In this combined chronic toxicity/carcinogenicity study (MRID 46542901), XDE-007 (Noviflumuron; 97.9% a.i.; Lot Nos. F0031-161 and F0031-148) was administered in the diet to Fischer 344 rats (65/sex/dose) at nominal dosages of 0, 0.1, 1.0, 75, or 300 mg/kg/day for up to 2 years. After one year, an interim sacrifice was performed on 10 rats/sex/dose. An additional 10 rats/sex/dose were treated at 0 or 1 mg/kg/day for up to 90 days to evaluate subchronic toxicity. A subchronic neurotoxicity phase examining the neuro-behavioral parameters was also included in this study.

B. Survival

Statistical analysis showed that there were no statistically significant survival disparities among the dose groups in male rats (Table 8); however, there was a statistically significant ($p<0.01$) decreasing trend for mortality in female rats (Table 9).

Table 8. Noviflumuron – Fischer 344 Rat Study (MRID No. 46542901)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks					Total
	1-26	27-52	52[i]	53-78	79-105[f]	
0	0/70	0/60[b]	10/60	2/50	17/48	19/60 (32)
0.1	0/60	0/60	10/60	1/50	11/49	12/50 (24)
1.0	0/70	0/60[b]	10/60	3/50	13/47	16/60 (27)
75.0	0/59[a]	0/59	10/59	1/49	14/48	15/49 (31)

300.0	0/60	1/60	10/59	3/49	10/46	14/50 (28)

+Number of animals that died during the interval/Number of animals alive at the beginning of the interval.
[i]Interim sacrifice at week 52.
[f]Final sacrifice at week 105.
[a]One accidental death at week 5, dose 75 mg/kg/day.
[b]Ten animals each in the control and 1.0 mg/kg/day dose groups were designated for a subchronic toxicity study and were sacrificed at 3 months.
( ) Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 9. Noviflumuron – Fischer 344 Rat Study (MRID No. 46542901)

Female Mortality Rates+ and Cox or Generalized K/W Test Results

Dose (mg/kg/day)	Weeks					Total
	1-26	27-52	52[i]	53-78	79-106[f]	
0	0/70	1/60[a]	8/59	1/50	8/49	10/62 (16)**[n]
0.1	0/60	0/60	10/60	1/50	13/49	14/50 (28)
1.0	0/70	0/60[a]	10/60	4/50	12/46	16/60 (27)
75.0	0/60	0/60	10/60	0/50	11/50	11/50 (22)
300.0	0/60	0/60	10/60	1/50	3/49	4/50 (8)

+Number of animals that died during the interval/Number of animals alive at the beginning of the interval.
[i]Interim sacrifice at week 52.
[f]Final sacrifice at weeks 105-106.
[n]Negative trend
[a]Ten animals each in the control and 1.0 mg/kg/day dose groups were designated for a subchronic toxicity study and were sacrificed at 3 months.
( ) Percent.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Tumor Analysis

Liver tumor incidence

The incidence of hepatocellular adenomas was increased in the 300-mg/kg/day males at 12 (2/10) and 24 months (16/50) relative to the controls (12 months, 0/10; 24 months, 6/50). Endometrial stromal polyps in the uterus were increased in the 75- and 300- mg/kg/day females (30/50 and 33/50, respectively) in comparison to the controls (15/50).

The statistical analyses using Fisher's Exact Test and the Exact Test for Trend demonstrated that in high-dose male rats (100 mg/kg/day), increases in the incidence of hepatocellular adenomas and adenomas and/or carcinomas combined had statistically significant trends and significant pairwise comparisons at $p < 0.01$ (Table 10).

Mesothelioma (in multiple organs)

Three cases of mesothelioma were noted in the 300-mg/kg/day males, whereas no mesothelioma was seen in the controls. The analysis showed a significant trend for mesotheliomas at $p < 0.05$ (Table 11) in high-dose male rats. However, the mesothelioma incidence was considered not to be treatment-related because: (1) there was no significant pairwise difference in incidence between any of the treatment groups and the control group; (2) the incidence for all groups was within the historical control range (1-7%) for male F344 rats in the National Toxicology Program (NTP) database; (3) this tumor type is common (i.e. not rare, background incidence >1%) in male F344 rats; and (4) there were no relevant non-neoplastic lesions to support this tumor type.

Endometrial stromal polyps

For female rats, the statistical analyses of the tumors were based upon Peto's Prevalence Test. Female rats had a statistically significant trend, and significant pair-wise comparisons of the 75 and 300 mg/kg/day dose groups with the controls, for uterine endometrial stromal polyps, all at $p < 0.01$. (Table 12).

Table 10. Noviflumuron – Fischer 344 Rat Study (MRID No. 46542901)

Male Liver Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	0.1	1.0	75.0	300.0	Historical Control
Adenomas (%) P =	6/60 (10) 0.0000**	2/60 (3) 0.9694	7/60 (12) 0.5000	7/59 (12) 0.4870	18[a]/59 (31) 0.0048**	2-4%[d]
Carcinomas (%) P =	1[b]/60 (2) 0.2260	1/60 (2) 0.7521	1/60 (2) 0.7521	0/59 (0) 1.0000	2/59 (3) 0.4936	0-6%[e] 0-3%

Combined	7/60	3/60	8/60	7/59	19[c]/59	
(%)	(12)	(5)	(13)	(12)	(32)	
P =	0.0000**	0.9527	0.5000	0.5984	0.0060**	

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
[a]First adenoma observed at week 52 in the 300 mg/kg/day dose group.
[b]First carcinoma observed at week 79 in the control group.
[c]One animal in the 300 mg/kg/day dose group had both an adenoma and a carcinoma.
[d] Represents 3 carcinogenicity studies (n=50-55) conducted with Fischer 344 rats by the performing lab since 2002.
[e] This range represents the NTP historical control range reported in 1990 because the sponsor did not provide historical data from the performing lab. Charles River Lab (animal supplier) historical control range was 0-3%.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$

Table 11. Noviflumuron – Fischer 344 Rat Study (MRID No. 46542901)

Male Mesothelioma Rates[+] and Fisher's Exact Test and Exact Trend Test Results

Dose (mg/kg/day)	0	0.1	1.0	75.0	300.0	Historical control
Mesotheliomas	0/60	1/60	0/60	2/59	3[a]/59	2.5%[b]
(%)	(0)	(2)	(0)	(3)	(5)	1-7%[c]
P =	0.02370*	0.50000	1.00000	0.24370	0.11872	

+: Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
[a:] First mesothelioma observed at week 99 in the 300 mg/kg/day dose group.
[b]: Charles River Lab (animal suppler) historical control data from a single study.
[c]: NTP HC 1-7%

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 12. Noviflumuron – Fischer 344 Rat Study (MRID No. 46542901)

Female Uterine Tumor Rates[+] and Peto's Prevalence Test Results

Dose (mg/kg/day)	0	0.1	1.0	75.0	300.0	Historical Control
Endometrial Stromal Polyps	15/50	13/50	16/50	30/50	33/50	8-37%[b]
(%)	(30)	(26)	(32)	(60)	(66)	0-42%[c]
P =	0.00003**	0.59134	0.24050	0.00186**	0.00044**	

+: Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor (week 69).

[a]: First polyp not in an interim sacrifice animal was observed at week 69 in the 0.1 mg/kg/day dose group.
[b]: NTP historical control
[c]: Charles River Lab historical control
Interim sacrifice animals have been excluded from this analysis. Polyp counts for interim sacrifice animals were 0, 3, 1, 0, 1, for the 0, 0.1, 1.0, 75 and 300 mg/kg/day dose groups, respectively.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

In summary, male rats at 300 mg/kg/day had treatment related increases in hepatocellular adenomas, and adenomas and/or carcinomas combined, and the increases showed statistically significant trends, and significant pair-wise comparisons relative to the controls, all at $p<0.01$. The incidence of endometrial stromal polyps in the 75-and 300-mg/kg females was also considered treatment-related based on statistical significance in both pairwise comparison and trend test and incidence greater than the historical and concurrent controls.

D. Non-neoplastic findings.

At 12-month of treatment, the only possible adverse finding was slight centrilobular/ midzonal hepatocyte hypertrophy in 75 mg/kg/day or above males.

Mean body weights of both males and females at the high dose (300 mg/kg/day) were decrease at various times (>10%). Increased incidence of lung inflammation was seen in 75 and 300 mg/kg/day males and females at 24 months (Table 13 and Table 14).

Increased incidences of gross tail papules were also noted in the ≥ 75 mg/kg/day males (42-50% treated vs 10% controls) and corresponded to increased very slight to moderate multifocal hyperkeratosis (45% treated vs 4% controls). At 300 mg/kg/day, increased incidences of gross tail papules were observed in females (Table 14), and tail necrosis was observed in the males. Increased incidences in the following effects were noted in the 300 mg/kg/day males on the tail skin and subcutis: (i) very slight to moderate focal hyperkeratosis; (ii) very slight to moderate multifocal hyperkeratosis; (iii) focal or multifocal hyperkeratosis; (iv) slight to severe focally extensive chronic active inflammation; and (v) focally extensive chronic active necrosis or inflammation. In the 300 mg/kg/day females, an increased incidence of focal or multifocal hyperkeratosis on the tail skin and subcutis was similarly observed.

Absolute and relative to body testes weights were increased in the ≥ 75 mg/kg/day (incr. 35-64%; except absolute weights at 75 mg/kg/day) at 24 months. Increased bilateral aspermia in the epididymides were noted at ≥ 75 mg/kg/day (76-78% treated vs 48% controls). The incidence and severity of very slight to severe seminiferous tubule atrophy was also increased at 300 mg/kg/day.

An increased incidence of uterine mass/nodule was observed in the ≥ 75 mg/kg/day females (54-74% treated vs 38% controls). Microscopically, these lesions were determined to be endometrial stromal polyps, and are discussed below under neoplasia.

Liver histopathology included the following findings: in the ≥ 75 mg/kg/day males, increased incidences and severity of basophilic foci of cellular alteration (total: 94% each treated vs 80% controls; 21 or more foci: 56-74% treated vs 0% controls) and in eosinophilic foci of cellular alteration (total: 78-88% treated vs 70% controls; 6-10 foci: 12-26% treated vs 2% controls) in the male rats at ≥ 75 mg/kg/day. Grossly, a single 300 mg/kg/day male had a liver nodule at 12 months, and an increase in liver foci at 300 mg/kg/day after 24 months of treatment.

Table 13. Incidence (# affected/# examined [%]) of selected non-neoplastic microscopic lesions in male rats treated with XDE-007 in the diet for up to 2 years.

Microscopic lesion		Dose (mg/kg/day)				
		0	0.1	1	75	300
Testes	Atrophy, seminiferous tubule, bilateral (total)	31/50 (62)	37/50 (74)	36/50 (72)	37/49 (76)	43/49* (88)
Epididymides	Aspermia, bilateral (total)	24/50 (48)	30/50 (60)	30/50 (60)	38/49* (78)	37/49* (76)
Skin and subcutis	Hyperkeratosis, with or without inflammation, tail, hair follicle, focal or multifocal (total)	6/50 (12)	16/29 (55)	10/32 (31)	20/38 (53)	30/50* (60)
	Necrosis or inflammation, chronic active, tail, focally extensive (total)	0/50 (0)	1/29 (3)	2/32 (6)	3/38 (8)	8/50* (16)
Liver	Focus of cellular alteration, basophilic (total)	40/50 (80)	44/50 (88)	43/50 (86)	47/50 (94)	47/50 (94)
	Focus of cellular alteration, eosinophilic (total)	35/50 (70)	42/50 (84)	35/50 (70)	39/50 (78)	44/50 (88)
	Hypertrophy, panlobular, hepatocyte (total)	2/50 (4)	0/50 (0)	1/50 (2)	38/50* (76)	43/50* (86)
Kidney	Hyperplasia, pelvic epithelium, unilateral (total)	2/50 (4)	4/50 (8)	3/50 (15)	9/50* (18)	14/50* (28)
	Hyperplasia, pelvic epithelium, bilateral (total)	0/50 (0)	0/50 (0)	1/50 (2)	2/50 (4)	3/50 (6)
	Mineralization, pelvic epithelium (total)	6/50 (12)	5/50 (10)	7/50 (14)	27/50* (54)	21/50* (42)
Lung	Inflammation, chronic, alveoli, focal or multifocal (total)	5/50 (10)	6/50 (12)	3/49 (6)	27/50* (54)	38/50* (76)

Table 14. Incidence (# affected/# examined [%]) of selected non-neoplastic microscopic lesions in female rats treated with XDE-007 in the diet for up to 2 years.

Microscopic lesion	Dose (mg/kg/day)				
	0	0.1	1	75	300
Skin and subcutis					
Hyperkeratosis, with or without inflammation, tail, hair follicle, focal (total)	1/50 (2)	1/18 (6)	0/17 (0)	0/13 (0)	5/50 (10)
Hyperkeratosis, tail, hair follicle, multifocal (total)	0/50 (0)	3/18 (17)	1/17 (6)	0/13 (0)	5/50 (10)
very slight					
Hyperkeratosis, with or without inflammation, tail, hair follicle, focal or multifocal (total)	1/50 (2)	4/18 (22)	1/17 (6)	0/13 (0)	10/50* (20)
Liver Hypertrophy with altered tinctorial properties, hepatocyte, centrilobular/midzonal	6/50 (12)	0/50* (0)	4/50 (8)	29/50* (58)	39/50* (78)
Lung Inflammation, chronic, alveoli, focal or multifocal (total)	15/50 (30)	10/50 (20)	10/50 (20)	41/50* (82)	47/50* (94)

E. Adequacy of Dosing for Carcinogenicity Assessment

Dosing was considered adequate based on non-neoplastic adverse effects found at the tumorigenic dose (300 mg/kg/day) level or the next lower dose (75 mg/kg/day). These effects included: decreased body weights, papules and hyperkeratosis on tails, bilateral aspermia in the epididymides, seminiferous tubule atrophy, and inflammation in the lungs.

In addition, in 2002 HED and DOW AgroSciences held a meeting to discuss the dose selections for chronic/carcinogenicity study in Fischer 344 rats, neurotoxicity study in rat, and carcinogenicity study in CD-1 mice (TXR 0050628, D281517; April 4, 2002). HED concluded that the dose levels selected for this study were reasonable and supported by the data presented by DOW AgroSciences at the meeting.

III. TOXICOLOGY

1. Metabolism

In a series of metabolism studies in rats (MRID 46277911), the data showed that with oral administration, at low dose (1 mg/kg), noviflumuron was absorbed at approximately 42 to 56% of the administered dose (AD), while at high dose (100 mg/kg) the absorption was markedly reduced to approximately 2-6% of AD, indicating the absorption process was saturated at high dose. In addition, absorption was also lower with repeated doing at approximately 35% of AD.

The majority of the absorbed radioactivity was found in the carcass. Radioactivity was also associated with the skin, liver, and kidneys. When radioactivity was normalized to tissue weight, the concentration of radioactivity was highest in the fat, generally followed by ovaries, adrenals, uterus, carcass, skin, liver, and kidneys.

Noviflumuron was metabolized via several pathways. The major process was cleavage of the acyl urea moiety followed by conjugation with glycine with the corresponding aniline metabolite being hydroxylated and conjugated with either sulfate or glucuronic acid. The metabolic process yielded the following metabolites: a ring-hydroxylated 2-fluoro-3,5-dichloro-4-(hexafluoropropoxyl) aniline (12% AD); deschloro-Parent (9% AD); 2,6-difluorobenzoic acid (32% AD); sulfate conjugate of ring-hydroxylated 2-fluoro-3,5-dichloro-4-(hexafluoropropoxyl) aniline (12% AD).

Majority of the absorbed radioactivity was eliminated via feces (64% AD), and urine elimination consisted of 16% AD. However, up to 29% AD was retained in tissues and carcass. A repeated-dose experiment indicates that the test article does not bioaccumulate beyond 19% AD.

2. Mutagenicity

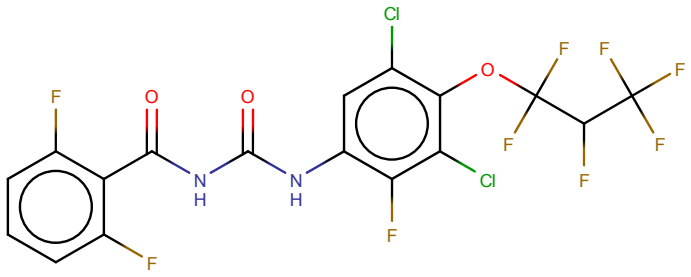
There is no mutagenic concern for noviflumuron in the available genotoxicity studies which were all shown to be negative. The studies include *in-vitro* bacterial mutation assay, a mammalian cell forward mutation assays, two *in-vitro* chromosome aberration tests, and an *in-vivo* mouse bone marrow micronucleus test, and they are summarized below:

Bacterial Reverse Mutation Test (*Salmonella typhimurium*)	45516717 (2001) ±S9: 33.3, 100, 333, 1000, 3300, & 5000 µg/plate	Negative. XDE-007 was tested up to concentrations where precipitation was observed (≥333 µg/plate).
in vitro Mammalian Cell Gene Mutation Test (Mouse Lymphoma Cells)	45516719 (2001) Acceptable / Guideline ±S9: 6.66, 12.5, 20, 25, 50, 66.6. 100, 200 µg/plate	Negative. Precipitation of test material was observed in both assays in the presence and absence of S9 (≥20 µg/mL).
in vitro Mammalian Chromosome Aberration Test (Primary Rat Lymphocyte)	45232418 (2000) Acceptable / Guideline ±S9: 0.5, 1.67, 5.0, 16.7, 50, 167, 500 µg/mL	Negative. Precipitation was observed (≥16.7 µg/mL).
	45516720 (2001) Acceptable / Guideline ±S9: 3.13, 6.25,12.5, 25, 50, 100, 200 µg/mL	Negative. Increasing degrees of precipitation up to the asserted limit of solubility of the test compound (200 µg/mL) were observed in the presence or absence of S9.

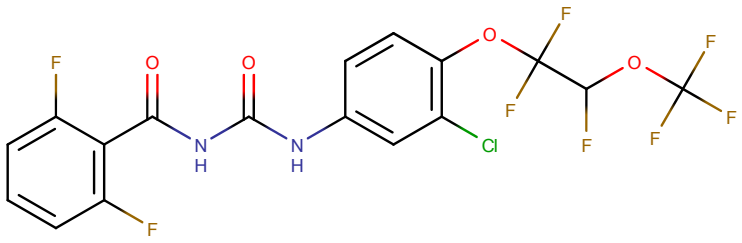
Mammalian Erythrocyte Micronucleus Test (Mouse)	45516718 (2001) Acceptable / Guideline M: 500, 1000, 2000 mg/kg/day	Negative.

3. **<u>Structure-Activity Relationship</u>:** Literature searches have been conducted, and at this time, the closest analogs are novaluron, lufenuron, and hexaflumuron. All of these compounds are chitin synthase inhibitors, as is noviflumuron. The three analogs have been shown previously to be non-carcinogenic.

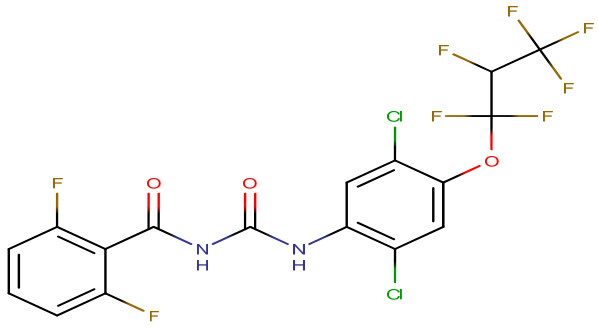
Noviflumuron:



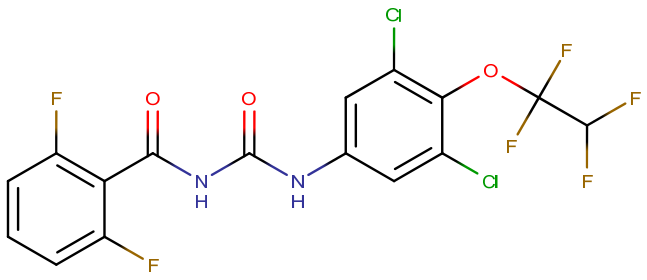
Novaluron:



Lufenuron:



Hexaflumuron:



4. Subchronic and Chronic Toxicity

Subchronic toxicity studies

28-day oral toxicity study in rats

In a subchronic toxicity study (MRID 45232416), XR-007 (99.6% a.i.; Lot/Batch no. DECO-615-112) was administered to 5 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 1, 10, 100, 500 or 1000 mg/kg bw/day (0, 1.0 10.4, 101.4, 512.6, 1029.1 mg/kg/day for males and 0, 1.1, 10.9, 105.1, 520.6, 1055.6 mg/kg/day for females) for 4 weeks. There were no compound-related effects on mortality, clinical signs, body weights, body weight gains, gross pathology, hematology, clinical chemistry, or urinalysis parameters.

There appeared to be a treatment-related effect on food consumption in males in the 1000 mg/kg/day group during the latter part of the study (days 23-28). All males in the 1000 mg/kg/day group consumed less diet than any of the controls (13.1-15.0 g/animal/day), and 2 of 5 males in the 1000 mg/kg/day group consumed less than half that amount (5.1 and 5.5 g/animal/day). Absolute liver weights were significantly increased at 500 and 1000 mg/kg/day in both sexes (males: 118 and 128% of controls, respectively; females:124 and 125% of controls, respectively). Relative liver weights were also increased in males at 500 and 1000 mg/kg/day (116 and 125% of controls, respectively), and in females in the 500 and 1000 mg/kg/day groups (118 and 120% of controls, respectively). Microscopic examination of the liver revealed very slight centrilobular hepatocellular hypertrophy in all 5 male rats and 5 female rats in the 1000 mg/kg/day dose group and in all 5 females in the 500 mg/kg/day group. The changes in liver weight correlate fairly well with the increased incidence of centrilobular hepatocellular hypertrophy in animals in the 500 and 1000 mg/kg/day groups, and are considered to be treatment-related. However, these liver changes are considered to be a non-adverse (adaptive) response to treatment.

The LOAEL is 1029 mg/kg/day based on decreased food consumption in males. The NOAEL is 513 mg/kg/day.

28-day oral toxicity study in mice

In a 28-day oral toxicity study (MRID 45516716), Noviflumuron (XDE-007) (98.4% a.i.; Lot/Batch no. F0031-148; TSN102332) was administered to 5 CD-1 mice/sex/dose in the diet at dose levels of 0, 10, 100, 500 or 1000 mg/kg/day (0, 10.8, 110, 538, 1060 mg/kg/day for males and 0, 11.2, 113, 504, 1140 mg/kg/day for females) for 28 days. There were no compound-related effects on mortality, clinical signs, body weights, body weight gains, food consumption, ophthalmology, or gross pathology.

Absolute liver weights were significantly increased in males and females in the 100 (127 and 112% of controls, respectively), 500 (122 and 124% of controls, respectively), and 1000 (130 and 126% of controls, respectively) mg/kg/day. Similarly, relative liver weights were significantly increased in males at 100, 500, and 100 mg/kg/day (120, 122 and 133% of controls, respectively), and in females at 500 and 1000 mg/kg/day (123 and 118% of controls, respectively). Treatment-related liver lesions were observed in males at 500 and 1000 mg/kg/day and females at 1000 mg/kg/day. Microscopic examination revealed hepatocellular hypertrophy with altered tinctorial properties (centrilobular/midzonal to panlobular) in males at 500 and 1000 mg/kg/day and very slight vacuolization (consistent with fatty change) of the periportal hepatocytes in males at 500 and 1000 mg/kg/day and in females at 1000 mg/kg/day.

The LOAEL is 110 mg/kg/day based on increased liver weights in both sexes, progressing to liver toxicity at higher dose levels. The NOAEL for this study is 10.8 mg/kg/day.

Chronic Oral Toxicity Studies

Combined chronic/carcinogenicity study in rats

In this combined chronic toxicity/carcinogenicity study (MRID 46542901), XDE-007 (Noviflumuron; 97.9% a.i.; Lot Nos. F0031-161 and F0031-148) was administered in the diet to Fischer 344 rats (65/sex/dose) at nominal dosages of 0, 0.1, 1.0, 75, or 300 mg/kg/day for up to 2 years. After one year, an interim sacrifice was performed on 10 rats/sex/dose. Also at one year, 10 rats/sex/dose were evaluated for chronic neurotoxicity; 5 of these rats were shared with interim sacrifice toxicity group. The details of the neurotoxicity study are reported in MRID 46277910 (submitted concurrently). In addition, 10 rats/sex/dose were treated at 0 or 1 mg/kg/day for up to 90 days to evaluate subchronic toxicity.

No adverse treatment-related effects were observed on mortality, food consumption, food efficiency, or on any ophthalmoscopic, hematological, clinical chemistry, or urinalysis parameters. No adverse treatment-related effects were noted in the subchronic study.

Body weights and clinical signs: At ≥ 75 mg/kg/day, increased incidences (in total animal days, treated vs controls) of general papules/pustules on the skin/fur/mucous membranes were observed in the males (117-147 vs 14) and perineal urine soiling was noted in the females (128-174 vs 49). Papules were observed first on Day 309; soiling on Day 85. Decreased body weights were noted in males (↓ 3-10%) and females (↓ 2-16%). Decreases were first observed on Day 120 and persisted until animal termination. Decreased body weight gains were also observed, and the magnitude of the decrease gradually grew with time. Overall (Days 1-729) body weight gains were decreased by 10-15% in each sex.

At 300 mg/kg/day, increased incidences of the following clinical signs were noted: (i) general papules/pustules on the skin/fur/mucous membranes were observed in the females; (ii) perineal urine soiling in the males; and (iii) sloughed/missing part of tail in the males.

Gross and non-neoplastic histopathology: At 24 months, increased incidences of gross tail papules were noted in the ≥ 75 mg/kg/day males (42-50% treated vs 10% controls) and corresponded to increased very slight to moderate multifocal hyperkeratosis (45% treated vs 4% controls). At 300 mg/kg/day, increased incidences of gross tail papules were observed in females, and tail necrosis was observed in the males. Increased incidences in the following effects were noted in the 300 mg/kg/day males on the tail skin and subcutis: (i) very slight to moderate focal hyperkeratosis; (ii) very slight to moderate multifocal hyperkeratosis; (iii) focal or multifocal hyperkeratosis; (iv) slight to severe focally extensive chronic active inflammation; and (v) focally extensive chronic active necrosis or inflammation. In the 300 mg/kg/day females, an increased incidence of focal or multifocal hyperkeratosis on the tail skin and subcutis was observed.

At 24 months, absolute and relative to body testes weights were increased in the ≥ 75 mg/kg/day (increased 35-64%; except absolute weights at 75 mg/kg/day). Increased incidences of bilateral aspermia in the epididymides were noted at ≥ 75 mg/kg/day (76-78% treated vs 48% controls). An increased incidence and severity of very slight to severe seminiferous tubule atrophy was noted at 300 mg/kg/day.

At 24 months, an increased incidence of uterine mass/nodule was observed in the ≥ 75 mg/kg/day females (54-74% treated vs 38% controls). Microscopically, these lesions were determined to be endometrial stromal polyps, and are discussed below under neoplasia.

Microscopically in the liver in the ≥ 75 mg/kg/day males, increased incidences and severity were observed at 24 months in basophilic foci of cellular alteration (total: 94% each treated vs 80% controls; 21 or more foci: 56-74% treated vs 0% controls) and eosinophilic foci of cellular alteration (total: 78-88% treated vs 70% controls; 6-10 foci: 12-26% treated vs 2% controls). Grossly, a single 300 mg/kg/day male had a liver nodule at 12 months, and an increased incidence of liver foci was noted in the 300 mg/kg/day males at 24 months.

Carcinogenicity in mice

In a carcinogenicity study (MRID 46539601), XDE-007 (Noviflumuron; 97.9% a.i.; Lot No. F0031-161) was administered in the diet to CD-1 mice (50/sex/dose) for up to 18 months. The doses were 0, 0.5, 3.0, and 30.0 mg/kg/day in males and 0, 0.5, 30.0, and 100 mg/kg/day in females.

No treatment-related effects were observed on body weights, body weight gains, food consumption, or on leukocyte or differential leukocyte counts, or during ophthalmoscopic examinations.

No mortality was observed in males at any dose level. In females, survival was significantly ($p \leq 0.05$) decreased at the high dose (100 mg/kg/day). Mortality occurred during treatment days 57-85 (4%) and days 85-112 (10%) when compared to controls (0%) for the same time period. The largest difference in cumulative mortality compared to controls occurred during Days 505-532 (52% treated vs 24% controls). An apparent cause of death/moribund condition could not be

determined in 20/28 of the 100 mg/kg/day females. Irrespective of dose group, lymphosarcoma and renal disease were frequently identified as causes of death. An increased incidence of tonoclonic convulsions was observed in the 100 mg/kg/day females (156 total animal days in treated vs 32 days in controls). Tonoclonic convulsions were first observed on Day 43 in this group and were last observed on Day 533, with the largest increase in incidence observed on Day 323 (47% treated vs 4% controls).

In the liver, increased weights relative to body liver weights ($p \leq 0.05$) were observed in the ≥ 3 mg/kg/day males and the ≥ 30 mg/kg/day females (↑10-33%), and absolute liver weights were increased ($p \leq 0.05$) by 16-27% at 30/100 mg/kg/day (M/F). Very slight to slight centrilobular/midzonal hepatocyte hypertrophy was observed (# affected/50 in treated vs controls) in the ≥ 3 mg/kg/day males (21-30 vs 14; $p \leq 0.05$ at 30 mg/kg/day) and the 100 mg/kg/day females (11 vs 4). Additionally, very slight diffuse panlobular hepatocyte hypertrophy was also observed in the 100 mg/kg/day females (3/50 treated vs 0/50 controls). These effects were considered adaptive non-adverse changes.

In the lung, very slight to moderate subacute to chronic inflammation was increased in the ≥ 3 mg/kg/day males (5/50 treated vs 2/50 controls [focal]) and the 30 mg/kg/day males (6/50 vs 0/50 [multifocal]). In the ≥30 mg/kg/day females, focal or multifocal aggregates of alveolar macrophages were increased (4-6/50 vs 0/50), and was significant ($p \leq 0.05$) at 100 mg/kg/day for multifocal aggregates. Additionally, generalized congestion was noted in the 100 mg/kg/day females (4/50 treated vs 0/50 controls). These minor changes were not considered to be adverse.

IV. MODE of ACTION STUDIES

No tumor mode of action data was submitted for noviflumuron.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The CARC considered the following in its weight of the evidence evaluation of the available data:

Mouse Tumors

- The liver tumors observed in high dose female CD-1 mice are considered treatment-related;
- The liver tumors in high dose male CD-1 mice are not considered treatment-related; and
- The lung tumors (bronchiolar-alveolar carcinomas) seen in high dose females are not considered treatment-related.

Rat Tumors

- The liver tumors (hepatocellular adenomas and carcinomas) seen in male Fischer rats are considered treatment-related;

- Treatment-related uterine tumors (endometrial stromal polyps) were seen at the high dose in Fischer 344 rats; and

- The increased incidence of mesothelioma in male rats was not considered treatment-related.

Overall, treatment-related liver tumors were seen in female mouse and male rat, and treatment-related uterine tumors were seen in the rat.

There is no concern for mutagenicity.

The closest to analogs to noviflumuron are novaluron, lufenuron, and hexaflumuron. The three analogs have been shown previously to be non-carcinogenic.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with EPA's Final Guidelines for Carcinogenic Risk Assessment (2005), CARC classified Noviflumuron as "Likely to be Carcinogenic to Humans" based on the occurrence of treatment-related liver tumors in female mice and male rats, and the occurrence of uterine tumors (endometrial stromal polyps) in rats.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The CARC recommends that a linear low-dose extrapolation approach (i.e., Q1*) be used for quantifying the cancer risk in humans for exposure to noviflumuron.

VIII. BIBLIOGRAPHY

MRID No.	CITATION
45232416	Lick, S.J., Crissman, J.W., and Cieszlak F.S. (1997). XR-007: 4 Week Dietary toxicity study in fischer 344 rats. Health and Environmental Research Laboratories. The Dow Chemical Company, Midland, Michigan 48674. Laboratory Project Study ID No. 971106. Oct. 9, 1997. Unpublished
45232420.	Linscombe, V.A. (1997). Screening of XR-007 in an *in vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes, performed at the Health and Environmental Research Laboratories of The Dow Chemical Company, Midland, (MI). Laboratory Study No. 971069, dated 16 June 1997. Unpublished.
45516716.	Yano, B.L. and Day, S.J. (2001). XDE-007: 28-day dietary toxicity study in CD-1 mice. Toxicology and Environmental Research and Consulting. The Dow Chemical Company. Midland, Michigan 48674. Laboratory Project Study ID No. 001248. June 12, 2001. Unpublished.
45516717	Mecchi, M.S. (2001): Amended Final Report: *Salmonella-Escherichia coli*/Mammalian Microsome Reverse Mutation Assay, Preincubation Method With a Confirmatory Assay, with XDE-007, performed by Covance Laboratories, Inc., (Covance), Vienna, VA, Covance Study No.: 22129-0-422 OECD (Dow Study ID: 011001) dated June 20, 2001; Amended July 26 and August 14, 2001. Unpublished.
45516718	Erexson, G. L. (2001): Final Report. Evaluation of XDE-007 in the *In Vivo* Mouse Micronucleus Assay, performed at Covance Laboratories (Covance) Vienna (VA), Covance Study No.: 22129-0-455 OECD (Dow Study No.: 011077), dated August 9, 2001. Unpublished.
45516719	Linscombe, V. A., and Beuthin, D.J. (2001): Evaluation of XDE-007 in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay, performed at the Toxicological and Environmental Research and Consulting Laboratory of The Dow Chemical Company, Midland (MI), Laboratory Project No. ID:011076, dated 26 July 2001. Unpublished.
45516720	Linscombe, V.A., Jachson, K.M. and Beuthin, D.J. (2001). Evaluation of XDE-007 in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes, performed at the Toxicological and Environmental Research and Consulting, Laboratory of the Dow Chemical Company, Midland (MI). Laboratory Project Study ID: 011071, dated July 23, 2001. Unpublished.
46539601.	Johnson, K.A. (2005) XDE-007: 18-month oncogenicity study in CD-1 mice. Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 021038, April 25, 2005. Unpublished.
46542901	Yano, B.L., M.D. Dryzga, J. Thomas (2005) XDE-007: Two-year dietary chronic toxicity/oncogenicity and chronic neurotoxicity study in Fischer 344 rats.

Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID.: 011168, April 22, 2005. Unpublished

TXR #: 0050628 Memorandum: W. Sette to J. Tavano, April 4, 2002. XDE-007: Dose selection for chronic/ oncogenicity and chronic neurotoxicity study in Fischer 344 rats and a carcinogenicity study in CD – mice.

Yano, B.L.and Day, S.J. (2002). XR-007: 90-day dietary toxicity in CD-1 mice. Report of Toxicology & Environmental Research and Consulting. The Dow Chemical Company, Midland, MI. *(This study was not submitted to the Agency, but it was briefly described in the study report in relationship to the finding of tonoclonic convulsion)*